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Association between Type 2 Diabetes Mellitus and Brain Atrophy: A Meta-Analysis (*Diabetes Metab J* 2022;46:781-802)

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We thank Dr. Min for his interest in our article "Association between type 2 diabetes mellitus and brain atrophy: a meta-analysis" [1]. We also thank the editor for this continued opportunity to discuss our article.

Dr. Min noted the shortage of available longitudinal studies on type 2 diabetes mellitus (T2DM) and brain atrophy, and the limited number of covariates included. This is partly due to some newer, larger, ongoing longitudinal studies, whose initial cross-sectional data could be included in our study, have not yet produced enough longitudinal data or published their analysis. We expect further understanding of brain structural changes over time associated with T2DM as longitudinal results from such studies become available. While cohort characteristics and data processing methods varied among the studies included, we included as many studies with volumetric data compatible with our meta-analysis as we could to warrant sufficient statistical power. Results from our study further complemented and expanded upon earlier reviews of T2DM-related brain atrophy using different data and methods [2,3].

Although many studies reported an array of covariates, a sufficiently large number of available studies are needed to investigate each covariate's correlation with T2DM-related brain atrophy. This limited our ability to include many covariates of interest. For example, we share Dr. Min's interest in T2DM-related local brain atrophy as biomarkers of various cognitive functions, as both T2DM and the related neurodegeneration might occur long before clinical symptoms manifest [4-6]. So far, fewer studies reported local brain changes in addition to global brain changes, and fewer yet that measured cognitive functions. How exactly does local brain atrophy at different brain areas predict respective cognitive functions deserves further investigation.

We are also interested in the potential effects of diabetic medications on brain atrophy and cognition. In the current study, most of the studies that could be included in our meta-analysis did not specify what type of oral antidiabetic drugs were taken, and there were not a sufficient number of studies on insulin either. We agree with Dr. Min that available studies on the relationship between diabetic medications, brain atrophy and cognition are inconclusive [7,8]. In addition to these, due to the chronic nature of T2DM and their long-term management, presence of common comorbidities such as cardiovascular diseases etc. and recently coronavirus disease (COVID), it is important to study the trajectories of brain changes associated with T2DM and the impact of comorbidities and their treatments on brain [9]. Future studies should elucidate the impact of T2DM as a potential risk factor for brain health and potential early interventions to prevent or reverse its adverse effects on cognitive health, while providing some insight into potential mechanisms of metabolism-related neurodegeneration and pathological changes.

In summary, we look forward to further studies on T2DM-related brain atrophy, especially those with data on more, specific covariates of interest such as comorbidities, medications,

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cognitive functions, etc. Again, we thank Dr. Min's appreciation of our work on this subject.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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